Exhibit 13

Ov ria C er d T l

A se-Con l S dy

*† B T U Y ‖
J K

Opportunities for genital exposure to talc were assessed in 215 white females with epithelial ovarian cancers and in 215 control women from the general population matched by age, race, and residence. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 ($P < 0.003$) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted relative risk of 3.28 ($P < 0.001$) compared to women with neither exposure. This provides some support for an association between talc and ovarian cancer hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. The authors also investigated opportunities for potential talc exposure from rubber products such as condoms or diaphragms or from pelvic surgery. No significant differences were noted between cases and controls in these exposures, although the intensity of talc exposure from these sources was likely affected by variables not assessed in this study.
***Cancer* 50:3 –3 6, 198 .**

THE POSSIBILITY that ovarian cancer may be caused by exposure to certain hydrous magnesium silicates such as talc and asbestos has been raised by several researchers.[1-3] The lack of epidemiologic studies regarding this hypothesis prompted us to investigate talc exposure in a case-control study of ovarian cancer.

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Supported by Grant Number 5-RO1 CA24209, awarded by the National Institutes of Health, DHEW.

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This study could not have occurred without the generous participation of many clinicians and institutions in the greater Boston area including: Dr. Emanuel Friedman of the Beth Israel Hospital, Drs. Robert Knapp and Thomas Griffiths of the Brigham and Women's Hospital and Sidney Farber Cancer Institute, Dr. Arthur Hassett of the Brockton Hospital, Dr. Joel Rankin of the Framingham Union Hospital, Dr. Edward Copenhaver of the Lahey Clinic Foundation, Dr. James Nelson of the Massachusetts General Hospital, Dr. Clement Yahia of the New England Deaconess Hospital, Dr. Lalita Gandbhir of the Pondville Hospital, Dr. James Whelton of Saint Elizabeth's Hospital, Dr. Stephen Alpert of the Salem Hospital, Dr. Richard Hunter of the University of Massachusetts Medical School. The superb clerical and technical assistance of Ms. Eileen McManus, Ms. Sally Cassells, and Ms. Christine Peters is also gratefully acknowledged.

Accepted for publication December 29, 1981.

Methods

The cases studied were women with ovarian cancer, diagnosed between November 1978 and September 1981 and identified through the pathology logs or tumor boards of twelve participating hospitals in the Greater Boston area. The study was restricted to English-speaking residents of Massachusetts ranging in age from 18 to 80 years. During the study period, 297 eligible cases were identified. Physicians denied permission to contact their patients in 13 instances. Fourteen patients declined to participate, and 14 other patients had died or moved before they could be contacted.

For each of the 256 interviewed cases, slides of the surgical specimens were reviewed by two authors (W.R.W. or R.E.S). Eighteen cases were excluded as nonovarian primaries. Each ovarian tumor was classified according to the Histological Classification of Ovarian Tumors of the World Health Organization.[4] The present analysis was restricted to 215 white women with epithelial cancers, including 39 with tumors of borderline malignancy and their matched controls.

Control cases were identified through the Massachusetts Town Books, annual publications that list residents by name, age, and address. Controls were selected randomly from those women who matched cases by precinct of residence, race, and age within two years. Additionally, it was required that a subject be excluded

0008-543X/82/0715/0372 $0.75

as a control if she had had a bilateral salpingo-oophorectomy, but subjects were not excluded because of prior hysterectomy or other types of pelvic operations. Women who had had pelvic operations were generally confident in their knowledge of whether their ovaries had been removed, but the nature of the operations could not be verified by hospital records in each instance. Women whose statements could not be verified were included or excluded on the basis of their recollection of the surgery. The 215 controls in this study were eventually obtained from a total of 475 potential controls identified through the Town Books. Fifty-six (12%) of the total could not be reached because they had moved, died, or had disconnected or unlisted phones. Twenty-nine (6%) of the total were ineligible because of a history of bilateral salpingo-oophorectomy, while 20 (4%) were of the wrong age or race or did not speak English. Of the total potential controls, 155 (33%) refused to participate. If the 215 cases are characterized as to ease of matching, 121 (56%) cases were matched with no refusals, 58 (27%) were matched after one refusal, and 36 (17%) were matched only after two or more refusals.

Interviews were conducted personally to assess a number of factors from the menstrual and reproductive history, medical and family history, and environmental exposures. This report will deal only with the results of several questions related to potential or definite talc exposure by way of contraceptive practices, operations, or perineal hygiene. Subjects were stratified by potential confounders described below, and adjusted relative risks associated with these exposures were calculated by the Mantel-Haenszel procedure as adapted by Rothman and Boice.[5] To accommodate other confounders as well as the matched design in the data collection, logistic analysis for matched data as described by Breslow *et al.*[6] was also employed.

Results

The average age (and standard error of the mean, SEM) for cases was 53.2 (1.0) years and for controls, 53.5 (1.0) years. Table 1 shows other characteristics of subjects. Controls were comparable to cases in educational level and religion. Cases and controls differed significantly in marital status and parity with parity being the more important discriminator between them. Sixty-four percent of the cases were postmenopausal at the time of diagnosis, whereas 60% of controls were postmenopausal. Of these, 15 cases and 20 controls had had an artificial menopause. Parity and menopausal status were considered important potential confounders in this analysis and were adjusted for as described above.

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (Total = 215) No.	Cases (Total = 215) %	Controls (Total = 215) No.	Controls (Total = 215) %
Educational level (completed college)	48	22.3	49	22.8
Religion (Roman Catholic)	126	58.6	128	59.5
Marital status (never married)	46	21.4	24	11.2
Nulliparous	78	36.3	39	18.1
Menopausal status (postmenopausal*)	137	63.7	129	60.0

* Postmenopausal at time of diagnosis for cases or for interview for controls.

Relative risks associated with potential talc exposure from contamination on rubber products are explored in Table 2. Although surgical gloves of recent vintage are dusted with starch, talc contamination may still be found.[7] Thus, a history of pelvic operations (appendectomy, cesarean section, hysterectomy, and other operations on internal genital organs other than bilateral salpingo-oophorectomy) was determined in cases and controls. Excluding operations associated with the diagnosis or treatment of the ovarian cancer among the cases, no excess in the occurrence of pelvic operations was noted. The greatest opportunity for talc exposure from surgery occurred before 1950, when talc was the

TABLE 2. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Potential Talc Exposure from Contamination on Rubber Products

Exposure	Cases Total	Cases No. (%) with exposure	Controls Total	Controls No. (%) with exposure	Crude	Adjusted *	95% Confidence limits
Pelvic surgery	215	78 (36.3)	215	75 (34.9)	1.06	1.17	(0.76–1.79)
Pelvic surgery (prior to 1950)	215	51 (23.7)	215	48 (22.3)	1.08	1.12	(0.69–1.82)
Use of condoms†	169	19 (11.2)	191	30 (15.7)	0.68	0.77	(0.41–1.44)
Use of diaphragm†	169	37 (21.9)	191	35 (18.3)	1.24	1.19	(0.69–2.05)

* Adjusted for parity (nulliparous, parous) and menopausal status (pre- and postmenopausal).

† Restricted to subjects who had ever been married.

TABLE 3. Relative Risks (RR) Associated with Using Talc for Storage Among Diaphragm Users* by Duration of Use of Diaphragm

Duration of diaphragm use	Cases: Total	Cases: No. (%) who used talc on diaphragm	Controls: Total	Controls: No. (%) who used talc on diaphragm	Crude	Adjusted RR†	95% Confidence limits
Total diaphragm use less than five years	13	6 (46.2)	21	8 (38.1)	1.39	1.82	(0.42-8.00)
Total diaphragm use five or more years	27	16 (59.3)	19	11 (57.9)	1.06	1.23	(0.36-4.17)
All users	40	22 (55.0)	40	19 (47.5)	1.35	1.56	(0.62-3.88)

* Includes all women who used diaphragm regardless of marital status.

† Adjusted for parity and menopausal status.

predominantly used dusting powder for surgical gloves. However, no significant excess of pelvic operations prior to 1950 was observed for cases.

The patients (cases) who, at sometime, had been married, chose condoms less frequently and diaphragms more frequently for contraception than the control group, but neither difference was statistically significant. Condom use is not necessarily associated with talc exposure. Not all brands of condoms are dusted with talc, and lubricants could affect the shedding of talc from the condom. Unfortunately, details on specific brands of condoms were not obtained. Similarly, talc exposure is not a necessary consequence of diaphragm use. We inquired specifically about the practice of dusting the diaphragm with talc for storage after use (Table 3). Among all subjects who had used a diaphragm, there was no significant excess of cases who regularly stored their diaphragm using talc, nor was any greater risk associated with this practice observed among women who had used the diaphragm for longer durations. Before the risk from this exposure can be adequately assessed, greater detail is needed including frequency of use and whether the powder was washed off prior to use. Furthermore, contraceptive jellies used with the diaphragm could affect the transport of talc in the genital tract.

Hygienic practices involving talc were also studied. Specifically, we inquired whether women had regularly used talc as a dusting powder on the perineum or regularly dusted sanitary napkins with talc (Table 4). Ninety-two (42.8%) of the cases had talc exposure by either or both of these routes compared with 61 (28.4%) of the controls. The adjusted relative risk was 1.92 ($P < 0.003$) with 95% confidence limits of 1.27–2.89 compared to subjects who had neither exposure. Sixty (27.9%) cases and 48 (22.3%) controls had either used talc for dusting or on napkins but not both. This difference yielded an adjusted relative risk of 1.55, which was of borderline significance ($P = 0.06$). The greatest risk occurred in women who had both exposures (use on the perineum and on napkins) compared to women who had neither exposure. Thirty-two (14.9%) of cases were in this category compared with 13 (6.0%) controls, for an adjusted relative risk of 3.28 ($P < .001$) and 95% confidence limits of 1.68–6.42. The histologic characteristics of tumors developing in women with perineal exposure to talc did not differ significantly from those in women without perineal exposure to talc (Table 5). In addition, the proportion of cases with tumors of borderline malignancy was identical among those with and without perineal exposure to talc. Twenty-two (18%) of 123 cases without the exposure had tumors of bor-

TABLE 4. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Talc Exposure in Perineal Hygiene

			Types of perineal exposure		
	No perineal exposure	Any perineal exposure	As dusting powder but not on napkins	On napkins but not as dusting powder	Both on napkins and as dusting powder
Cases (Total = 215)	123 (57.2%)	92 (42.8%)	43 (20.0%)	17 (7.9%)	32 (14.9%)
Controls (Total = 215)	154 (71.6%)	61 (28.4%)	34 (15.8%)	14 (6.5%)	13 (6.0%)
Crude rr	1	1.89	1.58	1.52	3.08
Adjusted RR*	—	1.92	1.55		3.28
95% confidence limits	—	(1.27-2.89)	(0.98-2.47)		(1.68-6.42)

* Adjusted for parity and menopausal status.

derline malignancy compared to 17 (18%) of 92 with the talc exposure.

D cu on

The argument linking talc and ovarian cancer includes four elements: the chemical relationship between talc and asbestos, asbestos as a cause of pleural and peritoneal mesotheliomas, the possible relation between epithelial ovarian cancers and mesotheliomas, and the ability of talc to enter the pelvic cavity. The mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them. Generic "talc" is seldom pure and may be contaminated with asbestos, particularly in powders formulated prior to 1976.[8,9]

Epidemiologic studies have clearly linked lung cancer and pleural and peritoneal mesotheliomas with asbestos exposure. [0] An excess of similar pulmonary lesions has been reported in talc workers and seems to be correlated with the amount of asbestos contamination in the talc deposits worked. Graham and Graham[1] were able to induce ovarian neoplasms in guinea pigs with asbestos and suggested that ovarian cancer could be related to asbestos exposure, noting the similarity between mesotheliomas and ovarian cancers. Parmley and Woodruff[12] further emphasized this similarity and popularized the pelvic contamination theory, which proposed that environmental carcinogens might enter the pelvic cavity via the genital tract. Years earlier it had been observed that inert carbon particles placed in the vagina immediately prior to hysterectomy could be recovered from the fallopian tubes.[13] Although greeted with skepticism, the finding of talc particles embedded in normal and abnormal ovaries suggests that talc is a substance that can enter the pelvic cavity via the vagina.[2]

Although no consensus concerning the risks of talc has emerged from letters, editorial and articles,[3,14-16] participants in the discussion have agreed upon the need for epidemiologic studies of ovarian cancer and talc exposure. In this case-control study of ovarian cancer of the epithelial variety, we investigated several sources of potential talc exposure. Among these, the only significant finding was an association between ovarian cancer and hygienic practices involving the use of talc on the perineum. It is especially notable that women who regularly had both dusted their perineum with talc and had used it on sanitary napkins had more than a threefold increase in risk compared to women with neither exposure. Several potential biases must be considered in interpreting this association.

The observation by Wynder *et a* [7] that menstrual characteristics may differ between women with ovarian cancer and controls might suggest that such differences may confound the association between perineal use of talc and ovarian cancer. We found that menstrual characteristics of cases and controls were virtually identical in this study. Fifty-three (24.7%) cases complained of moderate or severe dysmenorrhea compared to 56 (26.0%) controls. Twenty-five (11.6%) cases complained of irregular periods compared to 32 (14.9%) controls. The average numbers (and SEM) of days of flow and cycle length were, respectively, 4.9 (0.1) and 28.9 (0.3) days for cases and 4.9 (0.1) and 29.6 (0.3) days for controls.

Since entry of talc into the pelvic cavity is prevented by hysterectomy or tubal ligation, it might also be argued that the inclusion of subjects with pelvic surgery in the analysis may obviate any association between talc and ovarian cancer. It should be noted that such surgery generally occurred near the end of reproductive life for both cases and controls, probably after most significant talc exposure had already occurred. The exclusion of such subjects from the analysis did not substantially alter the observed associations. For example, the adjusted relative risk for the use of talc both on the perineum and sanitary napkins was 2.79 < 0.003) in the group without pelvic surgery compared to 3.28 observed for the entire group.

In terms of other confounders, the association persisted after adjustment for menopausal status and parity. We also applied multivariate logistic regression for paired observations.[6] The maximum likelihood estimate of relative risk associated with any perineal use of talc was 1.61 = 0.03) with 95% confidence limits of 1.04–2.49 after simultaneous adjustment for religion, marital status, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking.

Our sample of cases represents more than 50% of ovarian cancer cases diagnosed in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc. There is reason for concern that the high refusal rate among the controls may have introduced a selection bias among the controls. But,

when we restricted the analysis to the 121 cases who were matched without a control refusal, we again found a significant association between talc use and ovarian cancer. For women who had used talc both in dusting and on the perineum we found an adjusted relative risk of 2.44 ($P < 0.05$). Interviewer bias is also unlikely to explain the association. Of the 18 women who were initially interviewed as ovarian cancer cases but later excluded as having metastatic tumors to the ovary, only one (5.6%) had both perineal and napkin exposure as compared with 15% in cases and 6% in controls.

Experimental data which might bear on the carcinogenicity of talc come primarily from models using pleural implantation of various minerals in rats.[18] These data suggest that carcinogenicity is dependent primarily upon the shape of the particles with long thin fibers such as those occurring in crocidolite asbestos being most carcinogenic. Talc consists primarily of plates but may contain fibers, although voluntary guidelines to limit the content of asbestisform fibers in consumer talcums were proposed by the cosmetics industry in 1976. [9]

If talc is involved in the etiology of ovarian cancer, it is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates. With ovulation entrapment of the surface epithelium of the ovary into the ovarian stroma occurs. If present, talc or other particulates might be incorporated into these inclusion cysts. Apparently implantation of foreign bodies into the lumens of epithelial lined organs provides a favorable environment for carcinogenesis.[20] Alternatively, talc might serve to stimulate entrapment of the surface epithelium and act in the same way that "incessant ovulation" has been proposed as an etiologic factor for ovarian cancer. Given the histologic and clinical diversity of ovarian cancer, talc exposure is unlikely to be the only cause. Undoubtedly, reproductive experiences such as pregnancies and, perhaps, oral contraceptive use play a role in its etiology. [1-3] The possibility that talc exposure interacts with these variables deserves further investigation.

It is hoped that this report will stimulate further study of talc exposure in relation to ovarian cancer. Animal studies would be helpful to determine whether and under what circumstances ovarian tumors may be induced by various talc preparations. Epidemiologic studies should focus on opportunities for excessive vaginal contamination with talc such as when it is repeatedly used in perineal dusting powders or sprays and in or on tampons, sanitary napkins, or other products intended for intravaginal use. More precise details on the exact nature and frequency of the exposure and the amount and specific brand of powder used are essential. Opportunities for talc exposure are widespread and pervasive, [4] but that should not discourage epidemiologists from studying this potentially important exposure in relation to ovarian cancer.

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Exhibit 14

diabetologists and in major medical centers where funduscopic examination is done routinely and competently. However, in the office of the primary care physicians, where most diabetics in this country receive much of their care, annual examination of the fundi through *dilated* pupils regrettably is performed infrequently if at all. Given that circumstance, an abnormal tourniquet test result demands a competent funduscopic examination to rule out proliferative retinopathy, often by referral to an ophthalmologist. I wish to emphasize that I am not advocating that the tourniquet test replace regular funduscopic examination.

If Drs Aaby and Zegarra have a cost-effective strategy to ensure adequate annual examination of the 11 million diabetics in the United States "by a physician who can recognize early proliferative diabetic retinopathy," I would happily endorse it and discard the tourniquet test; until then, the tourniquet test will identify nine of every ten patients with diabetic retinopathy who need to be referred to such a physician. Many of these patients' conditions are currently undiagnosed until loss of vision occurs.

Decrease in capillary fragility with improved diabetic control noted in several patients was not meant to imply regression of diabetic retinopathy. Histological study, however, may confirm that the tourniquet test does accurately reflect the progression or regression of diabetic dermal microangiopathy. At present, the vascular or platelet abnormality causing capillary fragility in diabetes is unknown. I am currently involved in a study correlating the tourniquet test with fluorescein retinal angiography in those patients who do not have identifiable diabetic retinopathy on ophthalmoscopic examination.

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Talc and Ovarian Cancer

To the Editor.—Cramer and co-workers[1] recently reported observing an association between talc use and risk of ovarian cancer. We therefore examined data on talc use that two of us (L.M. and L.P.L.) had collected as part of a case-control interview study of epithelial ovarian cancer conducted from 1974 to 1977 in the Washington, DC, area.[2] The cases were 197 women with pathologically confirmed primary epithelial ovarian cancers treated in participating hospitals. The controls were 197 women treated at the same hospitals for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy. The controls were frequency matched to the cases on age, race, and hospital. The interviewers asked questions about reproductive and sexual history, medical history, drug use, and other exposures. Questions about talc use were added to the questionnaire after the study began, so 135 cases and 171 controls were asked about talc exposure.

Estimated Relative Risk of Ovarian Cancer, According to Reported Use of Talc

	Cases	Controls	Estimated Relative Risk	95% Confidence Interval
No talc mentioned	62	61	1.0	. . .
Any talc mentioned	67	100	0.7	0.4-1.1
No diaphragm used	92	118	1.0	. . .
Diaphragm used, no talc	14	11	1.6	0.7-3.7
Diaphragm, with talc	25	41	0.8	0.4-1.4
No body talc	77	84	1.0	. . .
Some body talc	54	78	0.8	0.5-1.2
"All over"	37	57	0.7	0.4-1.2
Genital*	7	3	2.5	0.7-10.0
Legs only	1	0	. . .	. . .
Not genital	6	8	0.8	0.3-2.5
Unknown where	3	10	0.3	0.1-1.2

*On genitals, sanitary napkins, or underwear.

The reported talc use among cases and controls is given in the Table. We estimated the relative risk to talc users as 0.7 (95% confidence interval [CI]=0.4 to 1.1). The estimate was unaffected by adjustment for race, age, and gravidity. Neither women who used talc on their diaphragms nor those who used it as body powder seemed to be at excess risk. Women who used talc as a body powder were asked how they used it. Among the ten who specifically mentioned use on sanitary napkins, underwear, or the genital area, the relative risk was estimated as 2.5, but the small number of exposed women yielded an unreliable estimate (95% CI=0.7 to 10.0).

Our data thus indicate no overall association between talc use and risk of ovarian cancer. Although a small group of women who specifically reported genital use of body talcum powders showed an excess relative risk, use of talc on a diaphragm, which would be the closest exposure to the ovaries, did not seem to elevate risk.

Chance, bias in selection or observation, or confounding may have influenced these estimates. One important potential bias to consider in this and Cramer's study is a difference between cases and controls in recollecting or reporting talcum powder use, especially in the genital area. Talc exposure was not a major focus of this study, and few data are available to assess the likelihood of recall bias. Such a bias could stem from cases' heightened awareness or from the fact that controls were interviewed in the hospital while most cases were interviewed at home. On the other hand, the questions about talc use were rather simple and unambiguous. Also, we noted that cases and controls were equally likely to report douching. Since reporting of use of douches might be subject to the same recall biases as talc use, this observation suggests that little recall bias operated. Another possible interpretation of our findings of no apparent effect of using talc on the diaphragm but some effect of perineal use of powder is that talc itself does not increase risk of ovarian cancer but that patients with ovarian cancer have or perceive a greater need for using body powder in the genital area, for reasons related either to the biology of the disease or to life-style. We agree with Cramer and co-workers that other epidemiologic data will be useful.

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Exhibit 15

AMERICAN JOURNAL OF EPIDEMIOLOGY Vol. 128, No. 6

Printed in U.S.A.

PERSONAL AND ENVIRONMENTAL CHARACTERISTICS RELATED TO EPITHELIAL OVARIAN CANCER

II. EXPOSURES TO TALCUM POWDER, TOBACCO, ALCOHOL, AND COFFEE

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Vaginal exposures to talc and other particulates may play an etiologic role in epithelial ovarian cancer. Surgical sterilization may protect against ovarian cancer by blocking entry of such particulates into the peritoneal cavity. The authors assessed histories of talcum powder use, tubal sterilization, and hysterectomy with ovarian conservation in 188 women in the San Francisco Bay Area with epithelial ovarian cancers diagnosed in 1983–1985 and in 539 control women. To investigate the roles of blood-borne environmental exposures on ovarian cancer risk, they assessed lifetime consumption of coffee, tobacco, and alcohol in these women. Of the 539 controls, 280 were hospitalized women without overt cancer, and 259 were chosen from the general population by random digit telephone dialing. Ninety-seven (52%) of the cancer patients habitually used talcum powder on the perineum, compared with 247 (46%) of the controls. Adjusted for parity, the relative risk (RR) = 1.40, $p = 0.06$. There were no statistically significant trends with increasing frequency or duration of talc use, and patients did not differ from controls in use of talc on sanitary pads and/or contraceptive diaphragms. Fewer ovarian cancer patients (7%) than controls (13%) reported prior fallopian tube ligation (RR, adjusted for parity, = 0.56, $p = 0.06$), and fewer patients (20%) than controls (28%) reported prior hysterectomy (RR = 0.66, $p = 0.05$). The protective effect of hysterectomy was confined to those who underwent this surgery 10 or more years prior to interview and to those who had not undergone prior tubal sterilization. Consumption of cigarettes and alcohol did not differ between cases and controls. By contrast, 11 (6%) cases never regularly consumed coffee, compared with 31 (11%) hospital controls and 26 (10%) population controls (RR, adjusted for smoking, = 2.2, $p = 0.03$, for the comparison using all controls). Overall, ovarian cancer risk among women who had drunk coffee for more than 40 years was 3.4 times that of women who had never regularly consumed coffee ($p < 0.01$). However, the data exhibited no clear trends in risk with increasing consumption. Although risk ratios relating duration of coffee drinking to ovarian cancer were unaffected by adjustment for several characteristics, further study is needed to exclude potential confounding by other unmeasured characteristics.

alcohol drinking; coffee; environmental exposure; hysterectomy; ovarian neoplasms; talc; tobacco; sterilization, tubal

Received for publication May 29, 1987, and in final form April 11, 1988.

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Several investigators have hypothesized a carcinogenic role for exposures of the ovarian epithelium to environmental agents that enter the pelvic cavity through the vaginal canal (1–7). Attention has focused on hydrous magnesium silicates such as talc and asbestos because of the similarity between epithelial ovarian cancers and mesotheliomas, which are caused by exposure to asbestos. The hypothesis predicts that talcum powder use on the perineum, on sanitary napkins, and on contraceptive devices increases ovarian cancer risk. It also predicts that tubal sterilization and hysterectomy without bilateral oophorectomy protect against the disease by preventing environmental carcinogens from contacting the ovarian epithelium.

There are few data regarding these predicted consequences of the hypothesis. Cramer et al. (8) reported that ovarian cancer patients were significantly more likely than nonhospitalized control women to use talcum powder on the perineum or on sanitary napkins. However, Hartge et al. (9) found no statistically significant differences in prior talc use between cases and a series of hospital controls. A cohort study (10) of women who had undergone tubal ligation noted four ovarian cancers versus 1.45 expected, after 22,000 person-years of follow-up ($p = 0.06$). The four published case-control studies that have examined the effects of hysterectomy without bilateral oophorectomy found cases to have a lower prevalence of hysterectomy than controls, indicating that hysterectomy is associated with decreased risk of ovarian cancer (11–14). Weiss and Harlow (15) suggested that this association may be due to screening for malignant or premalignant ovarian conditions at hysterectomy by physicians who do not routinely remove the ovaries. According to this hypothesis, women who pass such screening would have reduced subsequent ovarian cancer risk when compared with women who were not subjected to hysterectomy.

Data relating ovarian cancer to consumption of coffee, tobacco, and alcohol also are sparse and conflicting. One case-control study has shown a statistically significant association between coffee consumption and increased risk of epithelial ovarian cancer (16). This study compared cases with hospitalized control women, whose current coffee consumption may not represent that of women in the general population. Four other studies using hospitalized controls (17–20) and one using nonhospitalized controls (21) found weak, nonsignificant positive associations between risk of this disease and amount of usual coffee consumption at interview. It is important to determine to what extent these conflicting findings may be due to differences in recent coffee consumption between hospitalized and population-based control groups or to other sources of bias.

Cigarette smoking has been associated with increased ovarian cancer risk in one prospective study (22) but was unassociated with it in several case-control studies (16, 17, 21). Indeed, the case-control studies have found small (nonsignificant) reductions in risk among smokers. Generally, such studies have found no relation between alcohol consumption and ovarian cancer, although a recent large study found a reduction in risk associated with heavy drinking (23).

We present the results of a case-control study of histologically verified epithelial ovarian carcinoma in which cases' prior histories of talc use, tubal ligation, hysterectomy without bilateral oophorectomy, and consumption of coffee, tobacco, and alcohol were compared with those of women from the general population, as well as with those of hospitalized control women. All subjects reported lifetime habits of talc use, coffee drinking, cigarette smoking, and alcohol consumption. Sum-

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This work was supported by NIH Grant CA 35067.

mary measures of lifetime exposures are evaluated in relation to ovarian cancer risk.

Materials and Methods

Study subjects

Cases were residents of northern California aged 18 to 74 years who were diagnosed during the period January 1983 to December 1985 at one of the seven hospitals in Santa Clara County or at the University of California, San Francisco, Medical Center. The present report is restricted to 188 women with primary epithelial ovarian cancer.

Two groups of control women were selected. The first group consisted of women who were hospitalized in one of the hospitals to which cases were admitted. The second group was selected from the general population using random digit dialing telephone contacts. Both groups of women were matched to cases on age (within five-year intervals), race (white, black, oriental), and additional criteria described in the accompanying paper (24). A total of 188 ovarian cancer patients, 280 hospital controls, and 259 population-based controls participated.

Exposure data and statistical analysis

Study subjects participated in structured interviews in their homes conducted by trained interviewers to assess menstrual and reproductive history, medical and family history, and environmental exposures. Subjects were asked whether they had ever used talcum powder on the perineum, on sanitary pads, or on diaphragms. Subjects who responded affirmatively to any of these questions were asked about frequency and duration of use. Subjects also were asked whether they had ever drunk more than 10 cups of coffee in any one year. Subjects who responded affirmatively reported the ages when coffee drinking started and stopped, the total number of years of coffee drinking, and the number of cups usually consumed per day or per week either currently or prior to stopping. Similar questions were asked about cigarette smoking, provided that the subject had smoked at least 100 cigarettes during her life, and about consumption of alcoholic beverages, provided that she had ever consumed more than 10 such beverages in any one year.

Eligibility criteria, participation rates, and details of the statistical analysis are provided in the accompanying paper (24). Odds ratios are called relative risks, and all p values are two-tailed.

Results

Characteristics of the cases are compared with those of the two control groups in table 1. Population controls were somewhat younger, better educated, and more likely to be premenopausal than were cases and hospital controls. Furthermore, cases were less likely to have used oral contraceptives and had an earlier age at menarche and

Table 1

Characteristics of study participants, San Francisco Bay Area, 1983–1985

Characteristic	Cases (n = 188) (%)	Controls	
		Hospital (n = 280) (%)	Population (n = 259) (%)
Age (years)			
<40	10	10	15
40–49	30	29	29
50–59	26	28	27
60+	35	33	29
Race			
White	95	97	94
Education (years)			
>12	59	59	67
No. of term pregnancies*			
0	21	17	10
1–3	60	59	67
4+	19	24	23
Age (years) at menarche			
12 or less	48	44	46
Menopausal status			
Premenopausal	34	32	41
Natural menopause	45	33	38
Surgical menopause	22	35	21
Oral contraceptives			
Ever used	46	50	58

* 20 or more weeks gestation.

fewer term pregnancies than either control group. The latter findings are reported in detail in the companion paper (24).

Relative risks associated with talc use, tubal ligation, and hysterectomy were similar when cases were compared with hospital controls and with population controls. Therefore, for these variables, we report results only for cases versus the combined group of all controls.

Talc use

A greater proportion of cases (52 per cent) than controls (46 per cent) reported prior use of talcum powder on the perineum (relative risk (RR) = 1.40, $p = 0.06$). However, there was little difference between cases and controls in use of talc on sanitary pads and diaphragms, with relative risks of 0.93 ($p = 0.76$) and 0.95 ($p = 0.86$), respectively. Table 2 shows the distributions of cases and controls and relative risks for talc use directly on the perineum, on sanitary pads, and on contraceptive diaphragms, singly and in combination. The table provides no evidence of elevated risk associated with more than one form of talc use. None of the women in the study reported prior occupational exposures to talc or asbestos fibers.

We next examined whether risk increased with increased duration or frequency of use of talcum powder on the perineum. Since tubal ligation and hysterectomy prevent contact between the ovarian epithelium and exogenous agents in the vaginal canal, we excluded any perineal talc use after the date of tubal ligation or hysterectomy in calculating duration of use. As seen in table 3, 55 per cent of cases versus 59 per cent of controls reported such use for less than one year. The risk for talc use between one and nine years, relative to that among users of shorter duration, was 1.60 ($p = 0.05$). However, an increasing dose-response pattern was not apparent, with risk among long-term users of 10 or more years only 1.11 times that of the nonusers or users of less than one year ($p = 0.61$). According to the logistic model fit to the data, the overall increase in risk for any 10-year increase in duration of use was 1.01 ($p = 0.56$).

TABLE 3

Ovarian cancer risk by length of talcum powder use on the perineum, San Francisco Bay Area, 1983–1985*

Years of talc use*	Cases		Controls		Relative risk†	95% confidence interval
	n	%	*n*	%		
None	103	55	320	59	1.00	
1–9	34	18	72	13	1.60	1.00–2.57
10+	50	27	147	27	1.11	0.74–1.65
Unknown	1	1	0	0		
Total	188	100	539	100		

* Prior to tubal ligation or hysterectomy.
† Adjusted for parity.

TABLE 2

Ovarian cancer risk by type of talcum powder use, San Francisco Bay Area, 1983–1985

Type of talc use	Cases		Controls		Relative risk*	95% confidence interval
	n	%	*n*	%		
None	75	40	230	43	1.00	
Perineum only	22	12	55	10	1.45	0.81–2.60
Sanitary pads only	5	3	28	5	0.62	0.21–1.80
Diaphragm only	9	5	19	4	1.50	0.63–3.58
Any two of perineum, pads, and diaphragm	67	36	168	31	1.36	0.91–2.04
All three of perineum, pads, and diaphragm	1	1	9	2	0.35	0.04–2.94
Incomplete data	9	5	30	6		
Total	188	100	539	100		

* Adjusted for parity and oral contraceptive use.

The relation between ovarian cancer risk and usual frequency of talc use on the perineum is shown in table 4. Women who used talc an average of one to 20 times per month were not at significantly altered risk from those who used it less frequently (RR = 1.27, $p = 0.29$). Those who customarily used talc on the perineum 20 or more times per month were at 1.45 times the risk of women in the lowest use category ($p = 0.09$). The overall increase in risk associated with 30 applications per month was 1.30 ($p = 0.19$).

Tubal ligation and hysterectomy

To investigate further the hypothesis of a role for vaginal exposure to environmental carcinogens in the etiology of ovarian cancer, we examined the effect of tubal ligation and hysterectomy on risk for the disease. Seven per cent of cases and 13 per cent of controls reported a history of tubal ligation (RR = 0.53, $p = 0.05$). Relative risks for tubal ligation were less than one among nulliparous, uniparous, and multiparous women, indicating that the protective effect of such surgery on ovarian cancer risk cannot be explained by confounding due to its greater prevalence among parous women who are at reduced risk of the disease. The overall reduction in risk associated with tubal ligation, adjusted for parity, was 0.56 ($p = 0.07$).

Cases with tubal ligation tended to undergo this surgery at younger ages (mean age (± standard error) = 31.9 years (±0.5)) than did controls (34.2 years (±0.1)). This difference does not support the hypothesis that early tubal ligation confers greater protection to the ovaries by early termination of exposure from the vaginal canal. Relative to women without this surgery, the risk for women with tubal ligation within 10 years of interview was 0.35 (95 per cent confidence interval (CI) 0.12–1.02), while the risk for women who underwent the surgery more than 10 years before interview was 0.69 (95 per cent CI 0.32–1.50).

Table 5 shows that hysterectomized women experienced 0.66 times the risk of those without such surgery ($p = 0.05$), but it does not show any trend of decreasing protection with time since hysterectomy. Such a trend would be expected if the protective effect of hysterectomy reflected merely the removal of high-risk women from the hysterectomized population via selective oophorectomy as suggested by Weiss and Harlow (15). On the contrary, table 5 shows that protection is limited to women hysterectomized 10 or more years prior to interview. Overall, cases and controls did not differ significantly in the ages at which hysterectomy was performed. The mean age at hysterectomy among cases with such prior surgery was 40.1 years (± 0.3), while the corresponding age for controls was 39.7 years (±0.1).

The hypothesis that hysterectomy protects against ovarian cancer by blocking

TABLE 4

Ovarian cancer risk by usual frequency of talcum powder use on the perineum, San Francisco Bay Area, 1983–1985

Applications of talc per month	Cases		Controls		Relative risk*	95% confidence interval
	n	%	*n*	%		
None	97	52	312	58	1.00	
1–20	41	22	114	21	1.27	0.82–1.96
20+	44	23	101	19	1.45	0.94–2.22
Unknown	6	3	12	2		
Total	188	100	539	100		
Overall trend for 30 uses per month					1.30	0.88–1.92

* Adjusted for parity.

exogenous agents' access to the ovaries predicts that such surgery confers no benefit on women whose ovaries are already protected by prior tubal ligation. Table 5 shows relative risks associated with hysterectomy among women with and without prior tubal ligation. As predicted, hysterectomy failed to protect women who had undergone prior tubal ligation (RR = 2.56, $p = 0.45$), but it did protect those who had not (RR = 0.57, $p = 0.02$).

Table 6 shows the effects of perineal talc use separately among women with and without prior tubal ligation or hysterectomy. The highest risk was experienced by talc users without such surgery. The risk in

TABLE 5

Ovarian cancer risk after hysterectomy without bilateral oophorectomy, by time between hysterectomy and interview and by absence or presence of prior tubal ligation, San Francisco Bay Area, 1983–1985

	Cases		Controls		Relative risk	95% confidence interval
	n	%	*n*	%		
No hysterectomy	151	80	389	72	1.00	
Hysterectomy	37	20	150*	28	0.66	0.43–1.00
Time (years) between hysterectomy and interview						
1–9	15	8	42	8	1.01	0.54–1.89
10–19	11	6	66	12	0.47	0.24–0.92
20+	11	6	41	8	0.63	0.31–1.29
No prior tubal ligation						
No hysterectomy	141	81†	333	71†	1.00	
Hysterectomy	33	19	135	29	0.57	0.36–0.90
Prior tubal ligation						
No hysterectomy	10	71‡	56	79‡	1.00	
Hysterectomy	4	29	15	21	2.56	0.23–29.12

* Date of hysterectomy was unknown for one woman.
† Per cent of cases or controls with no prior tubal ligation.
‡ Per cent of cases or controls with prior tubal ligation.

TABLE 6

Ovarian cancer risk by perineal talc use and by history of surgical sterilization,† San Francisco Bay Area, 1983–1985

Talc use	Surgical sterilization†	Cases		Controls		Relative risk‡	95% confidence interval
		n	%	*n*	%		
No	No	70	37	182	34	1.00	
Yes	No	71	38	151	28	1.33	0.88–2.01
No	Yes	21	11	110	20	0.50*	0.29–0.88
Yes	Yes	26	14	96	18	0.75	0.43–1.29
No	Total	91	48	292	54	1.00	
Yes	Total	97	52	247	46	1.37§	0.97–1.95
Total	No	141	75	333	62	1.00	
Total	Yes	47	25	206	38	0.53*,‖	0.36–0.79

* $p < 0.01$.
† Tubal ligation or hysterectomy.
‡ Adjusted for parity.
§ Adjusted for parity and surgical sterilization.
‖ Adjusted for parity and talc use.

this group was 1.33 times that of women with neither history of talc use nor history of surgery ($p = 0.18$). By contrast, risk was lowest among women with a history of tubal ligation or hysterectomy who never regularly applied talc to the perineum (RR = 0.50, $p = 0.02$).

Table 6 shows that, regardless of talc use, women who underwent either tubal ligation or hysterectomy without bilateral oophorectomy experienced a risk of 0.53 ($p = 0.002$) compared with women without such surgery.

Cases and controls did not differ significantly in the prevalence of barrier contraceptive use, devices that prevent entry of semen into the peritoneal cavity. Risks for women who had used diaphragms and condoms were 0.81 ($p = 0.22$) and 0.91 ($p = 0.59$), respectively, relative to risk among nonusers. There was no trend in risk with exposure of the ovaries to semen, defined as sexually active time before tubal ligation or hysterectomy, minus duration of use of condoms and diaphragms.

Coffee, tobacco, and alcohol

Table 7 shows the distribution of cases and controls and relative risks by coffee consumption status (ever vs. never). The relative risk for any coffee consumption, adjusted for cigarette smoking, was 2.21 for both control groups combined ($p = 0.03$). The relative risk was 2.13 ($p = 0.06$) for cases versus hospital controls and 1.59 ($p = 0.24$) for cases versus population controls. The corresponding unadjusted relative risks were 2.03 for combined controls, 1.90 for hospital controls, and 1.51 for population controls (not shown).

Table 7 also shows that risk among coffee drinkers increases with increasing duration of coffee consumption. This trend is evident in both the comparison based on hospital controls and the one based on population controls. Overall, smoking-adjusted cancer rates among women who had consumed coffee for more than 40 years were 3.4 times those of women who had never consumed coffee ($p < 0.01$). Among coffee drinkers, each additional 10 years of coffee drinking conferred an 11 per cent increase in risk, according to the logistic function fit to the data ($p = 0.37$). These findings could be confounded by age despite the matching within five-year age groups. However, the results were similar when age was added to the regressions as a continuous variable.

Relations between ovarian cancer risk and amount of usual coffee consumption are shown in table 8. The table provides no evidence for a positive trend in risk with

TABLE 7

Ovarian cancer risk by years of coffee consumption, San Francisco Bay Area, 1983–1985

Years of coffee consumption	Cases		Controls				Relative risk†			95% confidence interval‡
			Hospital		Population		Cases vs. hospital controls	Cases vs. population controls	Cases vs. all controls	
	n	%	*n*	%	*n*	%				
None	11	6	31	11	26	10	1.00	1.00	1.00	
Any	177	94	249	89	233	90	2.13	1.59	2.21	1.10–4.41
1–14	18	10	27	10	34	13	1.57	0.65	1.45	0.59–3.57
15–24	32	17	43	15	36	14	1.81	1.69	2.18	1.00–4.79
25–39	62	33	105	38	98	38	2.36	1.70	2.26	1.06–4.85
40+	65	35	73	26	64	25	3.45*	2.54	3.41*	1.46–7.96
Unspecified	0	0	1	0	1	0				
Overall trend per 10 years among coffee drinkers							1.16	1.14	1.11	0.89–1.38

* $p < 0.01$.

† Adjusted for smoking (lifelong nonsmoker vs. ever smoker).

‡ Cases versus all controls.

frequency of coffee drinking, regardless of the control group used for comparison. Frequency was measured as usual number of cups consumed per day prior to disease onset for cases and hospital controls who were current coffee drinkers, and as usual number of cups per day prior to stopping for former coffee drinkers. The test for trend of increasing risk with increasing frequency among those who consumed coffee was not significant ($p = 0.91$).

Similarly, table 9 shows no trend in risk with total cups of coffee consumed prior to disease onset (cases and hospital controls) or prior to interview (population controls). We estimated total coffee consumption by multiplying each woman's reported duration of coffee consumption in years by her usual frequency of consumption in cups per day times 365. Among coffee drinkers, the test for trend in risk with increasing total consumption yielded a p value of 0.56.

Relative risks corresponding to the above measures of coffee consumption were unchanged by adjustment for other variables potentially associated with ovarian cancer including educational level, parity, oral contraceptive use, estimated years of ovu-

TABLE 8

Ovarian cancer risk by usual frequency of coffee consumption, San Francisco Bay Area, 1983–1985*

Cups/day	Cases		Controls				Relative risk†			95% confidence interval‡
			Hospital		Population		Cases vs. hospital controls	Cases vs. population controls	Cases vs. all controls	
	n	%	*n*	%	*n*	%				
0	11	6	31	11	26	10	1.00	1.00	1.00	
1	50	27	62	22	58	22	2.21	1.86	2.42	1.15–5.09
2–3	73	39	94	34	98	38	2.13	1.63	2.26	1.09–4.66
4+	54	29	93	33	77	30	2.02	1.56	2.07	0.97–4.38
Overall trend per cup/day among coffee drinkers							1.01	1.01	1.01	0.93–1.08

* Prior to stopping for ex-drinkers, and prior to hospitalization for current drinkers, among cases and hospital controls.

† Adjusted for smoking (lifelong nonsmoker vs. ever smoker).

‡ Cases versus all controls.

TABLE 9

Ovarian cancer risk by estimated total cups of coffee consumed, San Francisco Bay Area, 1983–1985

Cup-years* of coffee consumption	Cases		Controls				Relative risk†			95% confidence interval‡
			Hospital		Population		Cases vs. hospital controls	Cases vs. population controls	Cases vs. all controls	
	n	%	*n*	%	*n*	%				
0	11	6	31	11	26	10	1.00	1.00	1.00	
1–30	41	22	50	18	60	23	2.30	1.54	2.30	1.09–4.86
31–60	32	17	46	16	32	12	2.21	2.30	2.64	1.21–5.75
61–90	27	14	38	14	32	12	2.03	1.96	2.46	1.10–5.51
90+	77	41	114	41	108	42	2.42	1.60	2.28	1.08–4.78
Unknown	0	0	1	0	1	0				
Overall trend per 10 cup-years among coffee drinkers							1.01	1.01	1.01	0.99–1.03

* One cup-year equals 365 cups of coffee.

† Adjusted for smoking (lifelong nonsmoker vs. ever smoker).

‡ Cases versus all controls.

lation, and duration of contraceptive-free marriage.

The risk for cigarette smoking relative to lifelong nonsmoking, adjusted for coffee consumption, was 0.73 ($p = 0.08$) for the comparison based on combined control groups. Corresponding relative risks for the hospital and population comparisons were 0.65 ($p = 0.04$) and 0.84 ($p = 0.39$), respectively. Unadjusted relative risks and confidence intervals were similar. While the odds ratios associated with smoking were less than unity, few of them achieved statistical significance.

Cases did not differ from either control group in the prevalence of prior alcohol consumption. For the comparison based on all controls, the relative risk was 0.74 ($p = 0.14$). Furthermore, there was no evidence of a trend in risk with increasing duration or amount of alcohol consumption. Women who drank heavily (20 or more drinks per week) had a risk 0.66 times that of nondrinkers, but the reduction was not statistically significant ($p = 0.34$). None of these observations were altered by adjustment for cigarette smoking or coffee consumption.

Discussion

Genital exposures to talc and other agents

The rationale for suspecting talc as an ovarian carcinogen derives from its chemical relation to and natural occurrence with asbestos. Asbestos causes pleural and peritoneal mesotheliomas (25), which are histologically similar to epithelial ovarian carcinomas (6). Graham and Graham (2) showed that, in guinea pigs and rabbits, asbestos can induce ovarian epithelial hyperplasia similar to early epithelial tumors in women. Evidence suggesting a role for vaginal exposure to particulates in human ovarian carcinogenesis is twofold. First, Egli et al. (26) demonstrated that nonmotile inert carbon particles deposited in the vagina prior to hysterectomy can be recovered in the fallopian tubes. Second, Henderson and coworkers have found talc particles embedded in both normal and malignant ovarian tissue (27, 28). While these findings indicate that vaginal exposure to particulates can lead to deposition on the ovaries, they do not implicate such exposure in ovarian carcinogenesis, and data relating directly to this possibility are needed.

In a comparison of epithelial ovarian cancer cases and nonhospitalized controls in Boston, Cramer et al. (8) reported a relative risk of 1.92 ($p < 0.003$) for epithelial ovarian cancer associated with use of talcum powder on the perineum or on sanitary pads. By contrast, the results of a case-control study in Washington, DC (9) and those of the present study show neither a strong nor a consistent association between genital talcum powder exposure and ovarian cancer. In the present data, regular use of talc on the perineum was associated with only a marginally significant elevation in relative risk. Furthermore, there were no clear differences between cases and controls when other forms of genital talc exposure were considered, either singly or in combination. Although the data show a trend of increasing risk with increasing frequency of perineal exposure, the trend is not statistically significant, and there is no trend with duration of exposure. Thus, while these data do not exonerate talc as an ovarian carcinogen, neither do they provide strong evidence to implicate it.

Several sources of bias must be considered as possible explanations for the lack of strong findings related to talc, including the study's failure to interview all eligible ovarian cancer patients and a completely random sample of controls, as well as the potential pitfalls of combining the two control groups. Another source of bias is confounding by differential talc use among women with characteristics predictive of ovarian cancer. However, such confounding seems unlikely. For example, although Wynder et al. (14) reported that certain menstrual characteristics differ between women with ovarian cancer and controls,

we and others (8, 13) found no significant differences between cases and controls in any of several menstrual characteristics examined, including history of amenorrhea, irregular menstrual cycles, and midcycle pain.

An additional source of bias is random error in reported talc use, which tends to attenuate relative risk estimates. Some error seems likely. Nevertheless, there seems only a small probability that these data contain reporting errors large enough to obscure the twofold increase in risk noted by Cramer et al. (8) for talc use on the perineum and on sanitary pads. Further epidemiologic studies are needed to clarify the role of talc as carcinogen, cocarcinogen, or promoter of epithelial ovarian carcinogenesis.

Indirect evidence in support of an etiologic role for vaginal exposures to some exogenous substances derives from the reduced risk associated here with fallopian tube sterilization and hysterectomy, procedures that block entry to the pelvic area through the reproductive tract. Apart from talc and asbestos, vaginally introduced substances that may initiate or promote ovarian cancer include other particulates, semen, spermicidal foams or creams, and douche solutions. We are unaware of data implicating any of these substances.

The reduced risk associated in these data with prior tubal sterilization is inconsistent with the results of a historical prospective study of 666 women who had undergone tubal ligation (10). These women experienced a slight, marginally significant increase in ovarian cancer risk. However, the study involved only four cases of ovarian cancer.

Women tend to undergo tubal sterilization during the height of their reproductive years (on average, in the early fourth decade of life, for the present data). By contrast, hysterectomy is generally performed at the end of the reproductive years, probably after a large fraction of genital exposures have already occurred. It is therefore noteworthy that the protective effects of hysterectomy noted here were limited to surgery 10 or more years prior to interview. This finding fails to support the conjecture of Weiss and Harlow (15) that the protection of hysterectomy is an artifact due to selective removal of precancerous ovaries at the time of surgery. If such selection explained the association, one would expect to find, as those authors did, a decrease in the level of protection with increasing years since surgery. However, the present data show just the opposite trend. They also indicate that the benefits of hysterectomy are confined to women without prior tubal sterilization, a finding that supports an etiologic role for genital exposures to the ovaries.

Other explanations are possible for the protective effects of tubal ligation and hysterectomy, if the effects are not due to chance or bias. For example, these procedures may alter the levels and/or the cyclic variations of estrogen, progesterone, or the gonadotropins. Tubal sterilization has been shown to reduce subsequent serum and urinary estrogen levels, possibly by inducing localized hypertension at the ovary (29, 30). Some data (30, 31) suggest that hysterectomy with ovarian conservation also may reduce estrogen production. Elevated estrogen levels have been linked to breast cancer and could be involved in ovarian carcinogenesis, although there are few data to support this possibility (32, 33). Tubal sterilization and hysterectomy may protect by reducing ovarian estrogen exposure. Alternatively, some forms of tubal sterilization have been associated with subsequent increased frequency of abnormal or anovulatory cycles (34, 35). Since estimated number of ovulations has been associated with increased ovarian cancer risk (36, 37), tubal sterilization may protect by suppressing ovulation.

Coffee, tobacco, and alcohol

The present data provide some support for the hypothesis that coffee drinking in-

creases risk for epithelial ovarian cancer. Comparison of cases versus the combined group of both hospitalized and population-based controls suggests that current or former coffee drinkers experience double the risk of nondrinkers. The relative risk based on comparison of cases versus only the population-based controls was smaller (RR = 1.59) and did not achieve statistical significance. Nevertheless, its magnitude suggests that coffee may be implicated in increased risk for the disease.

The hypothesis is also supported by the dose-response relation noted between risk and duration of coffee drinking among those who had ever drunk coffee. Compared with risks for nondrinkers, smoking-adjusted risks increased from 1.45 for fewer than 15 years of coffee drinking to 3.41 for 40 or more years of consumption. Trends of increasing risk with increasing years of coffee drinking were evident in both hospital and population-based control comparisons and in both smoking-adjusted and unadjusted analyses.

Yet, no trends were evident with increasing amount of usual coffee consumption in cups per day, or with total lifetime consumption, estimated by multiplying reported years of consumption by reported amount of usual consumption prior to illness or cessation of coffee drinking. Instead, risk remained approximately constant at two to three times that of nondrinkers, regardless of amount consumed. This lack of dose response is consistent with the negative findings of other studies (17–20) for trend in risk with increasing coffee consumption at time of interview. The absence of trend noted here may be due to inaccuracies in reported usual consumption as a measure of average coffee drinking frequency. Such inaccuracies (if similar in magnitude between cases and controls) could mask evidence of a dose-response relation. The observed patterns of trend with duration of coffee drinking and lack of trend with frequency of consumption and total consumption would be consistent with a causal relation if women tended to report their duration of coffee drinking more accurately than they reported the amount they usually consumed.

The present observation of increased ovarian cancer risk among coffee drinkers could be due to several sources of bias. The first possibility is differences between cases and controls in some measured or unmeasured characteristics that are correlated with coffee drinking. Body size is an unlikely source of such confounding, because cases and controls were similar in several assessments of weight, height, and weight for height, as related to body size both at age 20 and in recent years. Relative risks for coffee consumption were not altered in multivariate analyses with other variables found to be predictive of ovarian cancer. These include parity, oral contraceptive use, and duration of contraceptive-free marriage.

Potential confounding by dietary factors must also be considered. Cramer et al. (21) found a statistically significant trend of increasing risk with increasing consumption of animal fat, after adjusting for body weight and parity. Absence of data on dietary fat consumption in the present study precludes examination of potential confounding by this factor.

Second, the stronger association noted when cases were compared with hospital controls could be explained by reduced coffee consumption among these controls after the onset of subclinical disease manifestations. However, a statistically significant trend in risk with years of coffee drinking was also noted when cases were compared with population controls. Furthermore, the two sets of controls had similar prevalences of prior regular coffee drinking. Therefore, the possibility of selection bias among hospital controls seems unlikely to explain the observations.

Third, cases may have overreported their coffee consumption relative to controls. However, this explanation also seems unlikely, in view of the absence of evidence

for such reporting bias in cases' reports of tobacco and alcohol consumption.

To date, seven case-control studies have examined the relation between coffee and ovarian cancer (16–21, and the present study). Of these, two (the present study and one in Italy (16)) found statistically significant elevations of risk among coffee drinkers, with relative risks ranging from 1.5 to 2.0. The remaining five studies, one in Greece (17) and four in the United States (18–21), found slightly and nonsignificantly elevated risks associated with coffee consumption. These disparities are not easily explained by differences in coffee constituents or in women among the different study areas.

It is difficult to propose biologically plausible causal mechanisms to explain the positive associations, if the associations are not due to bias or chance. Coffee consumption has been shown to increase urinary excretion of catecholamines (38–41), suggesting that coffee increases the activity of the adrenal medulla. Coffee consumption also may increase adrenal production of androstenedione. Since peripheral aromatization of androstenedione to estrone forms the primary source of estrogen in postmenopausal women (41), coffee consumption may alter ovarian cancer risk by increasing estrogen production after the menopause. Such a mechanism is speculative, however, in view of the sparsity of data implicating estrogens in ovarian carcinogenesis (32, 33).

Cigarette smoking was associated nonsignificantly with reduced ovarian cancer risk. This finding agrees with those of other case-control studies (16, 17, 21) but disagrees with an increased ovarian cancer risk found in a prospective study of women who smoke (22). The present data show no relation between ovarian cancer risk and duration of cigarette smoking.

The data also provide no evidence for any relation between alcohol consumption and ovarian cancer risk, which is consistent with results of other studies that have examined this issue (17, 20, 21). One large study (23) found that women who consumed 20 or more drinks per week had half the risk of women who did not drink. We also found reduced risk associated with such heavy drinking, but the association did not achieve statistical significance. The lack of significance may be due to small numbers in the present study; thus, the relation of alcohol consumption to ovarian cancer should be examined in larger series.

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Exhibit 16

AMERICAN JOURNAL OF EPIDEMIOLOGY Vol. 130, No. 2
Printed in U.S.A.

Brief Original Contributions

A CASE-CONTROL STUDY OF BORDERLINE OVARIAN TUMORS: THE INFLUENCE OF PERINEAL EXPOSURE TO TALC

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Harlow, B. L. (Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115), and N. S. Weiss. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol* 1989;130:390–4.

The authors interviewed 116 female residents of western Washington State with serous and mucinous borderline ovarian tumors diagnosed between 1980 and 1985 and questioned them on their use of hygienic powders. A sample of 158 control women from the same counties were identified through random digit dialing and were interviewed as well. Neither the perineal application of baby powder nor the perineal application of cornstarch was associated with an appreciably altered risk of borderline ovarian tumors. However, women who used deodorizing powders alone or in combination with other talc-containing powders had 2.8 times the risk (95% confidence interval 1.1–11.7) of women who had not had perineal exposure to powder. These results suggest that future studies of ovarian tumors in relation to the application of talc-containing powders should consider ascertaining the specific type(s) of powder used.

ovarian neoplasms; talc

In light of the marked differences in age-specific incidence and patient survival between borderline and malignant epithelial ovarian tumors (1), we conducted a case-control study of borderline ovarian tumors to determine whether etiologic differences between these low-grade tumors and their malignant counterparts exist as well. As part of this study, we sought to investigate the possible etiologic role of perineal exposure to talc.

Interest in talc as a potential ovarian carcinogen has grown from reports of occupational asbestos exposure and ovarian cancer (2–4). Mineral talc, similar in chemical composition to various asbestos minerals, is the common base for most dusting powders that women may apply to the perineum, sanitary napkins, or diaphragms prior to storage (5). Presently, three epidemiologic studies have examined the association between talc exposure and ovarian cancer (6–8).

MATERIALS AND METHODS

The Seattle-Puget Sound Cancer Surveillance System classifies borderline ovarian tumors according to the World Health Organization *International Classification of Diseases for Oncology* (ICD-O) (9). Female residents of three urban counties of western Washington State diagnosed as having a serous or mucinous borderline ovarian tumor (ICD-O codes 8,440–8,481) were identified from the files of this population-based cancer reporting system. Included were white women aged 20–79 years whose tumors were diagnosed during the years

Received for publication August 4, 1988, and in final form February 28, 1989.

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The authors thank Dr. Daniel W. Cramer for his helpful advice and comments.

1980–1985. Among those tumors subject to an independent pathology review (73 per cent), 83 of 88 (94 per cent) were confirmed as borderline ovarian tumors. Given the high degree of histologic agreement, we chose to include the additional 33 cases whose tumors had not been reviewed. Through random digit dialing, we identified a control group of white women who were similar to the cases with respect to age and county of residence. Controls who had undergone bilateral oophorectomy were excluded from the analysis. Further details of the study methods are described elsewhere (10).

Reproductive, sexual, and medical histories and information on perineal exposure to talc were obtained during an in-person interview. An open-ended question asked women to specify the type(s), but not the brand name(s), of powder they had used for perineal application after bathing, on sanitary napkins, and for diaphragm storage prior to diagnosis (or a similar date for controls). Affirmative responses were categorized either as one or more of three talc-containing powders (baby powder, deodorizing powder, and other or unspecified talcum or "dusting" powders) or as cornstarch.

We were successful in obtaining interviews from 116 cases (68 per cent of those eligible) and 158 controls (74 per cent of those eligible). A detailed discussion of response rates can be found elsewhere (10). Since previous studies (including ours) have reported an association of ovarian cancer risk in relation to reproductive history and exogenous female hormones, we controlled for age, parity, and the use of oral contraceptives during the analysis, by means of stratification (11).

Results

Women who reported any perineal use of dusting powders—either after bathing, on sanitary napkins, or for diaphragm storage—had an adjusted relative risk of 1.1 for developing a borderline ovarian tumor (95 per cent confidence interval (CI) 0.7–2.1) (table 1). We further examined this association according to both the specific method of exposure to dusting powders and the type of powder used. The analysis by method of use indicates that a smaller proportion of cases than controls used talc-containing powder or cornstarch for diaphragm storage. The risk associated with the use of talc-containing powders or cornstarch after bathing was 1.2 (95 per cent CI 0.6–2.6). Women who reported any use of talc-containing powder or cornstarch on sanitary napkins had a risk about double (relative risk (RR) = 2.2, 95 per cent CI 0.8–19.8) that of women who reported no talc use. This risk was the same for women who reported applying powder both after bathing and to sanitary napkins. No increase in risk was present among short- and long-term diaphragm users, the risk was not modified by the use of cornstarch versus other talc-containing powders, and there was no variation in risk with increasing number of days of use (not shown).

When we compared cases and controls by the type of powder used, there was no excess risk of borderline tumors among women who applied cornstarch, baby powder, or unspecified talcum powder alone or in combination to the perineum. However, women who applied deodorizing powders with or without baby powder (only baby powder was reported as a second powder in women who used deodorizing powders) had nearly three times the risk of developing a borderline ovarian tumor compared with women who reported no perineal use of powder (RR = 2.8, 95 per cent CI 1.1–11.7).

When we examined the type of powder used according to the method of application, the excess risk due to the use of deodorizing powders was present regardless of whether it was applied after bathing or to sanitary napkins. No subjects reported any use of deodorizing powders for diaphragm storage.

Discussion

Our results of perineal exposure to talc—no association among women who applied talcum powder to diaphragms, but a modest increase in risk among women who applied

TABLE 1

Perineal use of talc-containing powder and cornstarch among women with borderline ovarian tumors and their matched controls, by method of use and by type of powder used, western Washington State, 1980–1985

	Cases (n = 116)	Controls (n = 158)	Crude RR*	Adjusted RR†	95% CI*
No perineal exposure to powder	67	94	1.0‡		
Any perineal exposure to powder	49	64	1.1	1.1	0.7–2.1
Method of use					
Diaphragm storage only	8	21	0.5	0.5	0.2–1.4
Diaphragm storage only or with other methods	11	27	0.6	0.5	0.2–1.3
After bathing only	24	30	1.1	1.2	0.6–2.6
After bathing only or with other methods	34	37	1.3	1.3	0.8–2.7
Sanitary napkins only	7	4	2.5	2.2	0.8–19.8
Sanitary napkins only or with other methods	14	10	2.0	1.9	0.9–6.9
After bathing and on sanitary napkins	7	4	2.5	2.2	0.8–19.8
Type of powder used					
Cornstarch only (no combined use)	4	7	0.8	0.8	0.2–3.8
Baby powder only	18	31	0.8	0.8	0.4–1.9
Baby powder only or combined use	22	34	0.9	0.9	0.5–2.0
Talc, unspecified (no combined use)	18	19	1.0	1.0	0.4–2.4
Deodorizing powder only	10	4	3.5	3.5	1.2–28.7
Deodorizing powder only or combined use	14	7	2.8	2.8	1.1–11.7
Method and type of powder used					
Any powder use after bathing					
Any use of deodorizing powder	10	8	2.8	3.1	0.8–10.9
No use of deodorizing powder	24	32	1.1	1.1	0.5–2.4
Any powder use on sanitary napkins					
Any use of deodorizing powder	8	4	2.8	2.6	0.9–22.4
No use of deodorizing powder	6	6	1.4	1.5	0.4–6.5

* RR, relative risk; CI, confidence interval.

† Adjusted for age (20–39, 40–59, or 60–79 years), parity (nulliparous or parous), and use of oral contraceptives (ever or never).

‡ *Reference group.*

talc-containing powders to the perineum or to sanitary napkins—are consistent with those previously reported in studies of malignant ovarian tumors. Cramer et al. (6) observed a 50 per cent excess risk among women who used dusting powders or who applied talc-containing powders to sanitary napkins, and a relative risk of 3.3 among women who applied both. No association was found with use of talcum powder for diaphragm storage. Hartge et al. (7) also found no excess risk among users of talc for diaphragm storage, but they did report an association with perineal application (seven cases, three controls; RR = 2.5, 95 per cent CI 0.7–10.0). Whittemore et al. (8) reported a 40 per cent excess in risk of ovarian cancer associated with perineal exposure only and a modest increase in risk with increasing numbers of applications per month.

An association between talc use and ovarian neoplasms seems biologically plausible, since particulates contaminating the vaginal area may migrate into the pelvic cavity and since particles of talc have been observed within ovarian tissue (12–15). It is also conceivable that the excess risk as-

sociated with application of talc to the perineum and to sanitary napkins that was seen in the three prior studies, none of which inquired about the type of powder, could have been due to a strong association restricted to the use of deodorizing powders. The lack of an increased risk among women who used talc-containing powder on diaphragms (both in our study and in the previous studies) supports this hypothesis, since deodorizing powder was infrequently used for diaphragm storage. Furthermore, differential asbestos contamination among different types of cosmetic talcum powders cannot be ruled out. Until 1975, US-manufactured cosmetic talcum powders were required to contain at least 90 per cent mineral talc, but until 1968, some products marked as cosmetic talcum powders did not conform to these guidelines (16, 17). In 1976, a study of 21 consumer talcum powders labeled as baby powders, facial powders, or body powders obtained from retail stores in New York City between 1971 and 1975 reported that 10 contained concentrations of asbestiform tremolite and anthophyllite ranging from 0.2 per cent to 14 per cent (4).

Although it is difficult to explain the lack of association among women who used baby powder exclusively, according to the product labels baby powder is reported to contain only talc and no other minerals or deodorizing substances. The product labels from deodorizing powders, body powders, and perfumed dusting powders, on the other hand, indicate that they contain deodorizing substances and a variety of other free and bonded silicas (potentially high in asbestiform fibers (18)) in addition to talc.

We suggest caution when interpreting the results of this study. The elevated risk among women who specifically used *deodorizing* powders could have been due to chance or applicable only to borderline, not malignant, ovarian tumors. We believe the latter possibility to be unlikely, since the risk associated with the use of any talc-containing powder was similar to that reported in previous studies of women with malignant ovarian tumors. In addition, because of refusals and other reasons for nonparticipation, we were unable to include approximately 30 per cent of potentially eligible cases and controls. Since nonparticipants were similar to participants with respect to certain characteristics such as age and county of residence, we have no reason to believe that there was any dissimilarity in their use of talc-containing powders.

Given the clues provided by this study regarding the possible importance of deodorizing powders, it would be advisable for future studies to elicit information on the brand names of talc-containing powders and the timing and duration of use of each type of talc-containing powder. Although these data need replication, they raise the possibility that the risk of ovarian tumors in women who apply deodorizing powder to the perineum may not relate to talc per se but rather to asbestos contamination and/or a substance or substances used specifically for deodorization.

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